

EXHIBIT 2



U.S. Food and Drug Administration

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Department of Health and Human Services

Public Health Service
Food and Drug Administration
Silver Spring, MD 20993

TRANSMITTED BY FACSIMILE

Kurt Orlofski
CEO
Morton Grove Pharmaceuticals, Inc.
6451 West Main Street
Morton Grove, IL 60053

RE: ANDA # 88-191
Lindane Shampoo, USP, 1%
MACMIS ID # 15909

WARNING LETTER

Dear Mr. Orlofski:

This letter notifies Morton Grove Pharmaceuticals, Inc. (Morton Grove) that the Division of Drug Marketing, Advertising, and Communications (DDMAC) of the U.S. Food and Drug Administration (FDA) has reviewed promotional pieces for Lindane Shampoo, USP, 1% (Lindane Shampoo) issued by Morton Grove and by Alliant Pharmaceuticals, Inc. (Alliant), which until recently marketed Lindane Shampoo on behalf of Morton Grove.1 These pieces include websites promoting Lindane Shampoo (http://www.alliantpharma.com/alliant_products.html and <http://www.lindane4lice.com>)² and a promotional piece entitled *The Nit Picking News* (LINS 06-602). The websites and newsletter are misleading in that they omit and/or minimize the most serious and important risk information associated with the use of Lindane Shampoo, particularly in pediatric patients; include a misleading dosing claim; and overstate the efficacy of Lindane Shampoo. In particular, Lindane Shampoo is plainly labeled as second line treatment, suitable only when other, safer treatments fail or are not tolerated. The materials convey little sense of this limitation and little about the magnitude and nature of the risks associated with the drug. The materials appear to represent an attempt to downplay the significant risks associated with Lindane Shampoo use and encourage wider use, with less care, than is appropriate under approved labeling. These websites and newsletter thus misbrand Lindane Shampoo in violation of the Federal Food, Drug, and Cosmetic Act (Act), 21 U.S.C. 352(a) & (n) and 321(n), and FDA's implementing regulations. See 21 CFR 202.1(e)(3)(i); (e)(5); (e)(6)(i), (e)(7)(viii), & (e)(7)(x). We are very concerned about the potential for significant negative health consequences in children who use Lindane Shampoo because you are promoting Lindane Shampoo as being safer and more effective for pediatric patients than has been demonstrated by substantial evidence or substantial clinical experience, despite the boxed warning in Lindane Shampoo's FDA-approved product labeling (PI), and FDA's March 2003 Public Health Advisory³ and Talk Paper⁴ describing the risk of severe neurotoxicity in patients, including children, who weigh less than 110 pounds (50 kilograms).

Furthermore, while *The Nit Picking News* was submitted to FDA by Morton Grove under cover of Form FDA-2253, neither of the two websites were submitted to FDA under cover of Form FDA-2253, as required by 21 CFR 314.81 (b)(3)(i).

Background

The Indications and Usage section of the PI states (in relevant part):

Lindane Shampoo is indicated for the treatment of head lice (infestations of *Pediculosis humanis capititis*), crab lice (infestations of *Pthirus pubis*), and their ova only in patients who

1. cannot tolerate other approved therapies, or
2. have failed treatment with other approved therapies.

Lindane Shampoo should be used in the context of an overall lice management program that includes:

- Visual inspection to ensure that the patient is currently infested with live lice (empty egg casings or "nits" can remain on hair shaft long after true infestation).
- Manual removal of nits using a comb designed for this purpose and/or individual removal with tweezers followed by close examination of the hair and scalp.
- Evaluation and treatment of sexual contacts simultaneously. Sexual contacts should be prescribed Lindane Shampoo only if they either have failed to respond to adequate doses of other approved therapies or are intolerant of other approved therapies.
- All recently worn clothing, underwear, pajamas, used sheets, pillow cases, and towels should be washed in very hot water or dry-cleaned.

The PI for Lindane Shampoo includes a boxed warning relating to the risk of neurotoxicity associated with the use of this product. The boxed warning states:

WARNINGS:

Lindane Shampoo should only be used in patients who cannot tolerate or have failed first-line treatment with safer medications for the treatment of lice. (See INDICATIONS AND USAGE.)

Neurologic Toxicity

Seizures and deaths have been reported following Lindane Shampoo use with repeat or prolonged application, but also in rare cases following a single application according to directions. Lindane Shampoo should be used with caution in infants, children, the elderly, and individuals with other skin conditions, and those who weigh < 110 lbs (50 kg) as they may be at risk of serious neurotoxicity.

Contraindications

Lindane Shampoo is contraindicated in premature infants and individuals with known uncontrolled seizure disorders.

Proper Use

Instruct patients on proper use of Lindane Shampoo, the amount to apply, how long to leave it on, and avoiding re-treatment. Inform patients that itching occurs after the successful killing of lice and is not necessarily an indication for retreatment with Lindane Shampoo. (See DOSAGE AND ADMINISTRATION.)

The Contraindications section of the PI states (in relevant part):

Lindane Shampoo is contraindicated for premature infants because their skin may be more permeable than that of full term infants and their liver enzymes may not be sufficiently developed to metabolize Lindane.

Lindane Shampoo is also contraindicated for patients with crusted (Norwegian) scabies and other skin conditions (e.g. atopic dermatitis, psoriasis) that may increase systemic absorption of the drug.

Lindane Shampoo is contraindicated for patients with known uncontrolled seizure disorders and for individuals with a known sensitivity to the product or any of its components.

The Warnings section states (in relevant part):

Seizures and deaths have been reported following Lindane Shampoo use with repeat or prolonged application, but also in rare cases following a single application according to directions.

There have been cases of adverse events reported for Lindane Shampoo and Lindane Lotion in which a serious outcome (hospitalization, disability or death) has occurred. In approximately 20% of these cases, the shampoo and lotion were reported to have been used according to the labeled directions. Of these cases, thirteen deaths were reported, many of which were remote from the time of actual Lindane use. Lindane toxicity, verified by autopsy was the cause of one infant's death, and was the cause of death reported for an adult in a successful suicide. The direct causes of death for the other cases were attributed to reasons other than lindane. Most of these adverse events occurred with Lindane Lotion.

Infants, children, the elderly, and individuals with other skin conditions and those who weigh <1101bs (50 kg) may be at a greater risk of serious neurotoxicity. (See Pediatric Use and Geriatric Use.) Animal studies have shown increased susceptibility to neurologic adverse events in younger animals. Children have a larger body surface area to volume ratio that may result in a proportionately larger systemic exposure.

Careful consideration should be given before prescribing Lindane Shampoo to patients with conditions that may increase the risk of seizure, such as HIV infection, history of head trauma or a

prior seizure, CNS tumor, the presence of severe hepatic cirrhosis, excessive use of alcohol, abrupt withdrawal from alcohol or sedatives, as well as concomitant use of medications known to lower seizure threshold. (See PRECAUTIONS: Drug Interactions)

Patients should be instructed on the proper use of Lindane Shampoo, especially the amount to apply, how long to leave shampoo on, and the need to avoid retreatment. Patients should be informed that itching may occur after the successful killing of lice and repeat treatment may not be necessary.

The Precautions section of the PI includes the following directions (in relevant part) under "Information for Use":

- Use only enough Lindane Shampoo to lightly coat the hair and scalp.
- Apply shampoo directly to dry hair without adding water. Work thoroughly into the hair and allow to remain in place for 4 minutes only. Special attention should be given to the fine hairs along the neck and behind the ears.
- After 4 minutes, add small quantities of water to hair until a good lather forms.
- Immediately rinse all lather away. Avoid unnecessary contact of lather with other body surfaces.
- Towel briskly and then remove nits with nit comb or tweezers.
- There may be some Lindane Shampoo left in the bottle. Close the bottle with the leftover Lindane Shampoo and immediately throw away the bottle in a trash can out of the reach of children.
- Wash all recently worn clothing, underwear and pajamas, hats, and used sheets, pillow cases, and towels in very hot water or dry-clean.

The Nursing Mothers section of the PI states:

Lindane is lipophilic and is present in human breast milk, but exact quantities are not known. There may be a risk of toxicity if lindane is ingested from breast milk, or from skin absorption from mother to baby in the course of breastfeeding if Lindane Shampoo is applied topically to the chest area. Nursing mothers who require treatment with Lindane Shampoo should be advised of the potential risks and be instructed not to use the product on the skin as would be done for treatment of scabies. They should also be counseled to interrupt breastfeeding, with expression and discarding of milk, for at least 24 hours following use.

The Pediatric Use section of the PI states (in relevant part):

Infants and children may be at an even higher risk due to immaturity of organ systems such as skin and liver. Lindane Shampoo should be used with caution in patients who weigh less than approximately 110 lbs (50 kg) and especially in infants. Lindane Shampoo is indicated only for the treatment of lice; patients with scabies should use Lindane Lotion according to the labeled instructions.

Coinciding with the addition of the boxed warning to the PIs for Lindane Shampoo and Lindane Lotion, FDA released a Public Health Advisory in March 2003, addressing the significant potential toxicity associated with the use of topical formulations of Lindane Lotion for the treatment of scabies and Lindane Shampoo for the treatment of lice. An FDA Talk Paper was released at the same time on this topic discussing the significance of this risk from a public health perspective given the prevalence of head lice and scabies, which occur mostly in school-aged children.

These significant risks are further emphasized in the Medication Guide for Lindane Shampoo. The Medication Guide is a labeling feature reserved for products that the FDA determines pose a serious and significant public health concern requiring distribution of FDA-approved patient information.

Omission/Minimization of Risk Information

Promotional materials are misleading if they fail to reveal material facts with respect to consequences that may result from the use of the drug as recommended or suggested by the materials. Promotional materials also are misleading if they fail to include a balanced presentation of information relating to risks associated with the use of a drug along with the presentation of promotional claims relating to the effectiveness of the drug. The websites promoting Lindane Shampoo and the mailing piece are misleading because they make prominent claims of effectiveness for Lindane Shampoo for the treatment of head lice in children but omit and/or minimize important risk information from the body of the pieces, including crucial facts about potentially fatal risks associated with the use of Lindane Shampoo in this vulnerable population. This omission of risk information is completely at odds with the current labeling for Lindane Shampoo, which describes a drug associated with potentially fatal risks.

The Alliant "Our Products" web page is misleading in failing to include **any** risk information regarding treatment

with Lindane Shampoo, and in failing to note that it is indicated as a second line therapy. One of the principal messages of this web page is that Lindane Shampoo offers safe and effective treatment for head lice in all children, a message plainly at odds with labeling. For example, this product page prominently displays the tagline, "It's more than just CARING - It's caring about OUR KIDS' HEALTH" (emphasis original).

In fact, as stated in its PI, Lindane Shampoo should be used with caution in children because its use has been associated with seizures and death, and because of this risk it is second line treatment. Neither this risk nor any other risk information for the drug is disclosed anywhere on this website. Although the "Our Products" web page states, "Please see black box warning and other important safety information by clicking on the link below." this statement fails to provide appropriate qualification or pertinent information for the claims made on the website and the link to a separate website does not mitigate the misleading omission of risk information from this website. We are particularly concerned that this web page makes claims about improving the lives of children such as the above, yet fails to warn that children can die from using Lindane Shampoo.

Similarly, the Lindane Shampoo website home page and the linked web pages entitled "About Lindane Shampoo" and "Patients & Parents," focus on the use of Lindane Shampoo for pediatric patients. Specifically, the Lindane Shampoo website includes the smiling faces of two children on each web page, and both the content and title of the "Patients and Parents" page promotes use of the drug in children, for example, by stating, "The overwhelming majority of these infestations occur in children from 3 to 15 years of age." These web pages fail to include information on the risks associated with the use of Lindane Shampoo, and completely omit risks associated with the use of Lindane Shampoo in children. Although the "Patients and Parents" web page states: "It is important to follow the directions from the physician closely as in most cases these medications contain pesticides which if used or administered incorrectly may cause harm. Patients who are pregnant or breast feeding must alert their doctor as some products may not be suitable for their treatment." this page fails to include other important risk information, including the risks associated with the use of this product in patients who weigh less than 110 pounds (50 kilograms). There are links on the "About Lindane Shampoo" and "Patients and Parents" web pages to a PDF document entitled "Medication Instruction Guide" (LINS222 05/05), which contains some risk information, but the link to this document does not mitigate the misleading omission of risk information from these web pages.

Furthermore, your "Medication Instruction Guide" is itself misleading because it fails to present risk information with a prominence and readability reasonably comparable to the presentation of information relating to the effectiveness of Lindane Shampoo, and fails to reveal material facts with respect to consequences that may result from the use of Lindane Shampoo as recommended. This document presents application instructions using bolded headers and colorful graphics but presents risk information on the bottom right hand side of the web page in very small font. Furthermore, the document omits additional, important risks associated with Lindane Shampoo. For example, it fails to convey that a patient should not use Lindane Shampoo while breastfeeding as it is present in human breast milk and may cause toxicity if ingested from breast milk. The PI states that nursing mothers who require treatment with Lindane Shampoo should pump their breast milk and discard it for at least 24 hours after using the drug.

In addition, we note that, while the boxed warning about Lindane Shampoo does appear on the linked web pages entitled "Healthcare Professionals" and "Important Safety Information," these pages fail to disclose other important risk concepts not covered in the boxed warning, including but not limited to, the contraindications in patients with crusted (Norwegian) scabies and other skin conditions (e.g. atopic dermatitis, psoriasis). While there is a link to the PI on the "Healthcare Professionals" web page, this link does not mitigate the misleading omission of important risk information on these pages. Finally, some of the included risk information is incorrect. Specifically, these web pages state that Lindane Shampoo is contraindicated in "individuals with known **controlled** seizure disorders" (emphasis added). In fact the contraindication in the PI is for individuals with "known **uncontrolled** seizure disorders" (emphasis added).

Finally, the mailing piece entitled *The Nit Picking News*, which is directed at school nurses, fails to reveal material facts with respect to consequences that may result from the use of Lindane Shampoo as recommended or suggested in the material. In the box entitled "LINDANE facts," the *Nit Picking News* has a bullet which states, "FDA has determined that Lindane products have benefits that outweigh risks when used as directed. **Most serious adverse events reported in association with lindane products have been due to misuse.**" (emphasis original, footnote omitted) This bulleted statement is quoted from a paragraph of FDA's March 28, 2003, Public Health Advisory and cites to this advisory; however, this paragraph of the Public Health Advisory goes on to state:

However, there have been rare case reports of serious reactions with apparently normal use. These reports highlight the need to emphasize the potential toxicity of Lindane in the product labels and educate healthcare providers and patients about the risks and how to minimize them, as well as to develop mechanisms to facilitate safe use, once the drug is dispensed to patients. These mechanisms include having Lindane products available only in small packaged amounts to avoid excess application and requiring that the Medication Guide be given to the patient by the pharmacist with each new prescription. 5(Emphasis original.)

This mailing piece thus omits critical information reflected in the Public Health Advisory and in the PI for Lindane Shampoo regarding the risks of the drug associated with normal use (which include seizures and death). We note that the boxed warning is presented below the "LINDANE facts" box across the bottom of pages two and three of the piece; this, however, is not sufficient to overcome the misleading suggestion created by this claim that serious adverse reactions will not occur when Lindane Shampoo is used as directed.

Misleading Dosing Claim

The promotional piece entitled *The Nit Picking News* includes the claims:

- Effective treatment with any good pediculicide requires at least two treatments 5 to 7 days apart, to assure that both adult lice and eggs are killed by the treatment.
- Regardless of what treatment you choose, the most important "rules" to follow when trying to cure head lice are . . .Retreat in 5-7 days (one treatment will not cure).

These dosage recommendations contradict the PI and the Medication Guide, and are extremely alarming given that re-treatment with Lindane Shampoo can lead to increased exposure and possibly death. The boxed warning in the PI states, "Instruct patients on proper use of Lindane Shampoo, the amount to apply, how long to leave it on, and avoiding re-treatment. Inform patients that itching occurs after the successful killing of lice and is not necessarily an indication for retreatment with Lindane Shampoo." The Dosage and Administration section states, "Do not retreat." and the Medication Guide states, "Do not use Lindane Shampoo more than 1 time to treat an attack of lice. Do not use Lindane Shampoo to treat a second attack that comes soon after the first episode. No one knows a safe time to reuse Lindane Shampoo." These claims are particularly concerning given that the risk of neurotoxicity is amplified in many school aged children, the patient population you are targeting in this promotional piece directed at school nurses, because of their larger body surface area to volume ratio.

Overstatement of Efficacy

The Lindane Shampoo website implies that a patient can treat head lice quickly with Lindane Shampoo. For example, it claims:

- Lindane Shampoo is a highly effective topical prescription product for head lice that works in JUST 4 MINUTES!
- Lindane Shampoo has a FAST treatment time for head lice. . .it works in just 4 MINUTES!
(Emphasis original)

These claims misleadingly suggest that patients utilizing Lindane Shampoo will achieve treatment success in only four minutes. However, treatment of head lice includes considerably more effort than just a four minute application of Lindane Shampoo. As clearly stated in several parts of the PI (see Background section) and the Medication Guide, Lindane Shampoo should be used in the context of an overall lice management program that includes a four minute application time for Lindane Shampoo in combination with towel drying, manual removal of nits using a nit comb or tweezers, and washing of all recently worn clothing, underwear, pajamas, used sheets, pillowcases, and towels. A lice management program is an extremely time consuming and very labor intensive process. Simply applying Lindane Shampoo for four minutes will not successfully treat the infestation. Therefore, these claims overstate the effectiveness of Lindane Shampoo by suggesting that Lindane Shampoo treats head lice in just four minutes.

The "Our Products" page on the Alliant Website claims, "Lindane Shampoo has shown an efficacy rate of 92% at seven days and 85% at 14 days." (footnote omitted) This claim cites to an article that was published in the *American Journal of Diseases of Children* in 1986.⁶ However, as observed with antibiotic use and the development of resistant bacteria over time, Lindane use over several decades has helped to select resistant lice which are more difficult to treat successfully today than at the time this study was published in 1986.⁷ Recent reviews consistently include comments such as "Resistance to lindane is widespread and has resulted in decreased efficacy in the United States."⁸ It is our understanding that efficacy of Lindane has waned over time because of the increasing resistance of lice to this drug. If you have other, more recent data to support these claims, please submit them to FDA for review.

Failure to Submit

FDA regulations require the applicant to submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of initial publication of the advertisement for a prescription drug product. Each submission is required to be accompanied by a completed transmittal Form FDA-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use) and is required to include a copy of the product's current professional labeling. Neither the Alliant product web page (http://www.alliantpharma.com/alliant_products.html) nor the Lindane Shampoo website (<http://www.lindane4lice.com>) were submitted to FDA on Form FDA-2253, as required by 21 CFR 314.81(b)(3)(i).

Conclusion and Requested Action

For the reasons discussed above, the websites and newsletter misbrand Lindane Shampoo in violation of the Act and FDA's implementing regulations. 21 U.S.C. 352(a) & (n); 321(n); see also 21 CFR 202.1 (e)(3)(i); (e)(5); (e)(6) (i); (e)(7)(viii) & (e)(7)(x). Finally, the websites were not submitted to FDA under cover of FDA Form-2253, as required by 21 CFR 314.81(b)(3)(i).

DDMAC requests that Morton Grove, and any third party marketing Lindane on behalf of Morton Grove, immediately cease the dissemination of violative promotional materials for Lindane Shampoo such as those described above. We are extremely concerned by this promotion, which targets pediatric patients who are at

particular risk with respect to this drug.

Please submit a written response to this letter on or before December 31, 2007, stating whether you intend to comply with the above request, listing all violative promotional materials for Lindane Shampoo the same as or similar to those described above, and explaining your plan for discontinuing use of these materials. Because the violations described above are serious, we request, further, that your submission include a comprehensive plan of action to disseminate truthful, non-misleading, and complete corrective messages about the issues discussed in this letter to the audience(s) that received the violative promotional materials. Please direct your response to me at the Food and Drug Administration, Center for Drug Evaluation and Research, Division of Drug Marketing, Advertising, and Communications, 5901-B Ammendale Road, Beltsville, MD 20705-1266, facsimile at:301-796-9877. In all future correspondence regarding this matter, please refer to the MACMIS #15909 in addition to the ANDA number. We remind you that only written communications are considered official.

The violations discussed in this letter do not necessarily constitute an exhaustive list. It is your responsibility to ensure that all your promotional materials comply with each applicable requirement of the Act and FDA implementing regulations.

Failure to correct the violations discussed above may result in FDA regulatory action, including seizure or injunction, without further notice.

Sincerely,

/S/

Thomas W. Abrams, R.Ph., M.B.A.
Director
Division of Drug Marketing,
Advertising, and Communications

1 A June 12, 2007, press release from Sciele Pharma, Inc., (found on the Internet at http://phx.corporate-ir.net/phoenix.zhtml?c=120763&p=irol-newsArticle_print&ID=1014610&highlight=) announced that Sciele Pharma, Inc. had completed its acquisition of Alliant Pharmaceuticals, Inc. and indicated that Alliant and Morton Grove terminated the agreement between the two companies pursuant to which Alliant marketed lindane. The websites promoting Lindane Shampoo were available for several weeks following this press release.

2 FDA staff last accessed the Alliant website on August 8, 2007 and the Lindane Shampoo website on July 2, 2007. We note that both the Lindane Shampoo website [<http://www.lindane4lice.com>] and the Alliant website [<http://www.alliantpharma.com>] can no longer be accessed through these URLs.

3 "FDA Public Health Advisory: Safety of Topical Lindane Products for the Treatment of Scabies and Lice," dated March 28, 2003, FDA's Drug Information Page on Lindane, located at <http://www.fda.gov/cder/drug/infopage/lindane/lindanePHA.htm> (PHA).

4 "FDA Talk Paper -- FDA Issues Health Advisory Regarding Labeling Changes for Lindane Products," dated March 28, 2003, FDA's Drug Information Page on Lindane, located at <http://www.fda.gov/bbs/tonics/ANSWERS/2003/ANSO1205.html> (Talk Paper).

5 "FDA Public Health Advisory: Safety of Topical Lindane Products for the Treatment of Scabies and Lice," dated March 28, 2003, FDA's Drug Information Page on Lindane, located at <http://www.fda.gov/cder/drug/infopage/lindane/lindanePHA.htm> (PHA).

6 Brandenburg K, Deinard AS, DiNapoli J, et al. 1% permethrin cream rinse vs 1% lindane shampoo in treating Pediculosis capitis. Am J Dis Child. 1986;140(9):894-896.

7 See, e.g., Meinking, TL, Am J Manag Care. 2004 Sep;10(9 Suppl):5264-8; Meinking TL, Taplin D. Advances in pediculosis, scabies, and other mite infestations. Adv Dermatol. 1990;5:131-50. The authors of this 1990 publication concluded that considerable evidence had accumulated indicating that lice can become tolerant or resistant to lindane.

8 Burkhardt, et al., Expert Opin Drug Saf 2006;5(1):173.

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